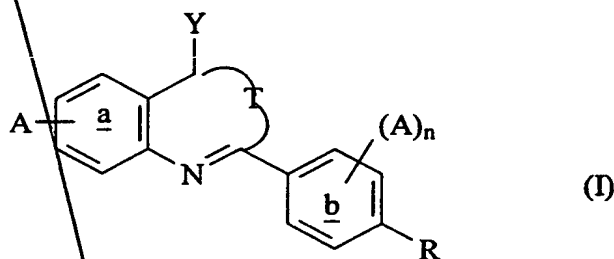


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CLAIMS

1. Use of an inhibitor of dihydroorotate dehydrogenase in the manufacture of a medicament for use in the treatment of an infection attributable to a virus of the
5 Flaviridae, Rhabdoviridae or Paramyxoviridae family.
2. Use according to claim 1, wherein the inhibitor is a compound of the formula (I):



wherein:

- each A is independently selected from the group consisting of hydrogen, halogen,
10 perhaloalkoxy, amino C₁-C₈ alkyl, NO₂, CN, SO₂CH₃, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, aryl, aryloxy, C₁-C₆ perhaloalkyl and Y; or
two adjacent groups A on ring b form, together with the phenyl ring to which they are attached, a naphthalene ring system;
- R is cyclohexyl, phenoxy or benzoxy, or a phenyl ring which is unsubstituted or
15 substituted by a group A as defined above; or
R and an adjacent group A on ring b form, together with the phenyl ring to which they are attached, a naphthalene or phenanthrene ring system;
- Y is selected from the group consisting of COOM, CONHR', SO₃M and hydrogen;
M is selected from the group consisting of H, Li, Na, K and 0.5 Ca;
- 20 R' is C₁-C₁₀ alkyl;

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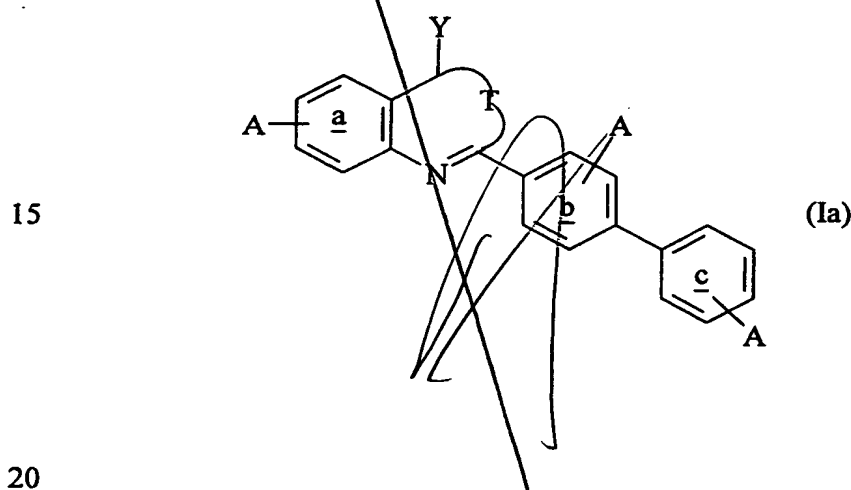
n is 1 or 2; and

T is =N- or =C(Z)- wherein either:

(i) Z is selected from the group consisting of hydrogen, NH_2 , OH, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, aryl and $\text{C}_1\text{-C}_6$ perhaloalkyl, or

5 (ii) Z is a bridging moiety selected from the group consisting of -V-W- (wherein V is CH_2 or S and W is CH_2 , O, S or NH) and $-(\text{CH}_2)_2\text{-C(=Z)-}$ wherein Z is O or H_2 , the said bridging moiety being attached to the ortho position of ring b of the adjacent biphenyl group, thereby completing a ring.

3. Use according to claim 2, wherein the inhibitor is a compound of
10 formula (Ia):



wherein:

each A is independently selected from the group consisting of hydrogen, halogen, amino $\text{C}_1\text{-C}_8$ alkyl, NO_2 , CN, SO_2CH_3 , $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, aryl, $\text{C}_1\text{-C}_6$

25 perhaloalkyl and Y;

Y is selected from the group consisting of COOM, CONHR', SO_3M and hydrogen;

M is selected from the group consisting of H, Li, Na, K and 0.5 Ca;

R' is $\text{C}_1\text{-C}_{10}$ alkyl; and

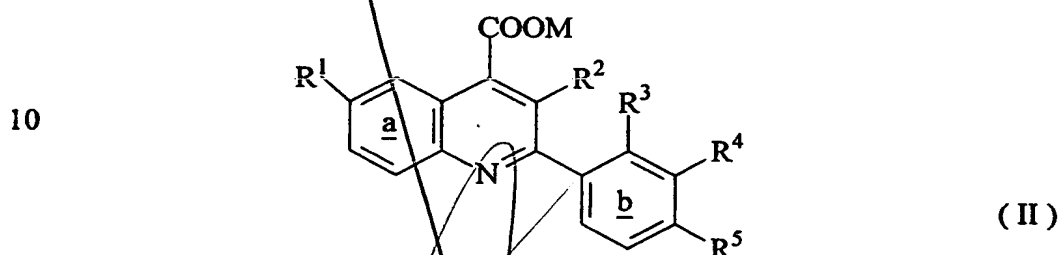
T is =N- or =C(Z)- wherein either:

30 (i) Z is selected from the group consisting of hydrogen, NH_2 , OH, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, aryl and $\text{C}_1\text{-C}_6$ perhaloalkyl, or

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(ii) Z is a bridging moiety selected from the group consisting of -V-W- (wherein V is CH₂ or S and W is CH₂, O, S or NH) and -(CH₂)₂-C(=Z)- wherein Z is O or H₂, the said bridging moiety being attached to the ortho position of ring b of the adjacent biphenyl group, thereby completing a ring.

- 5 4. Use according to claim 2 or 3 wherein the inhibitor is a compound of the formula (II):



15

wherein

R¹ is H, a halogen or OCF₃;

R² is H or C₁-C₆ alkyl;

R³ is H or OR⁶ wherein R⁶ is H or C₁-C₆ alkyl;

- 20 R⁴ is H or C₁-C₆ alkyl; or R⁴ and R³ form, together with phenyl ring b to which they are attached, a naphthalene ring; and

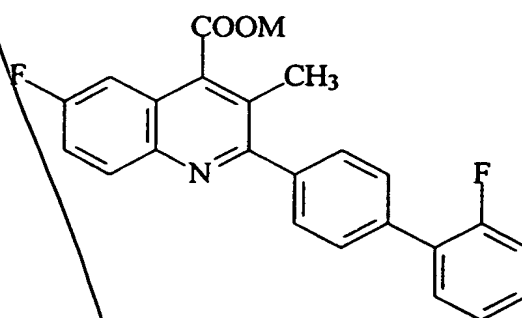
R⁵ is cyclohexyl, phenyl or benzyloxy, or a phenyl ring which is unsubstituted or substituted by halogen; or R⁴ and R⁵ form, together with phenyl ring b to which they are attached, a phenanthrene ring.

25

5. Use according to any one of claims 2 to 4 wherein the inhibitor is a compound of formula (IIb):

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5

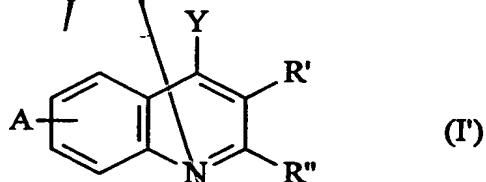


(IIb)

10 wherein M is H or Na.

6. Use according to claim 1 wherein the inhibitor is a compound of formula (I'):

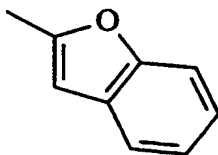
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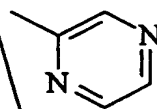
(I')

wherein A and Y are as defined above for formula (I);

15 R' is hydrogen and R'' is a thiophene ring or a group of formula (i') or (ii'):



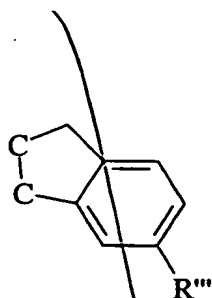
(i')



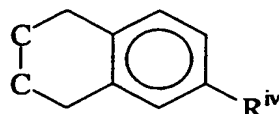
(ii')

or R' and R'' form, together with the carbon atoms (denoted "C") to which they are attached, a ring system of formula (iii') or (iv'):

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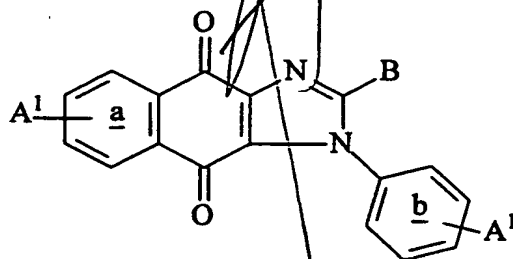
(iii')



(iv')

10 wherein R''' is H or halogen and R^{iv} is H or C₁ - C₆ alkoxy.

7. Use according to claim 1, wherein the inhibitor is a compound of the formula (III):

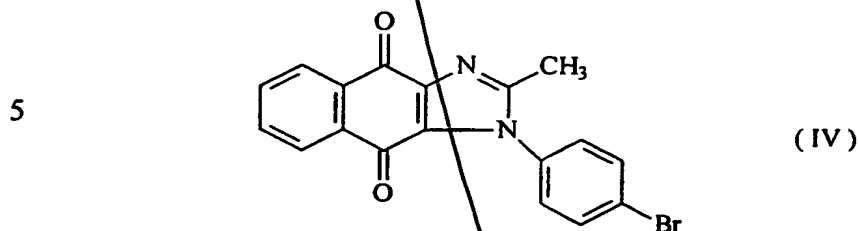


(III)

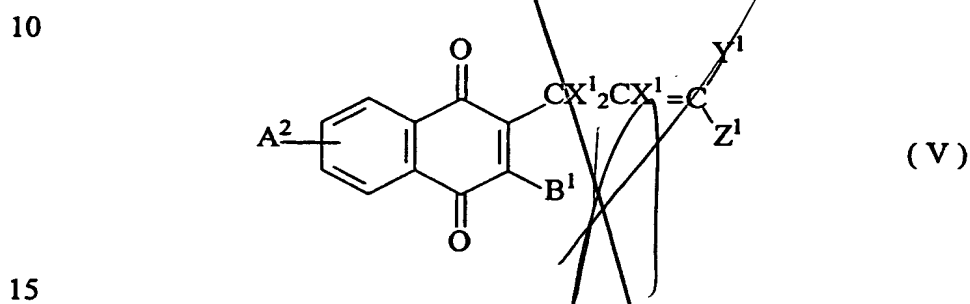
wherein:

each A¹ is independently selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₇ cycloalkyl, halogen, unsubstituted aryl, X-substituted aryl, NO₂, CN, COOR, CONHR and NHR;
 25 X is selected from the group consisting of halogen, NO₂, C₁-C₈ alkyl, aryl, fused aryl and COOR;
 R is selected from the group consisting of hydrogen and C₁-C₈ alkyl; and
 B is selected from the group consisting of C₁-C₈ alkyl, H, CF₃ and aryl which is
 30 unsubstituted or substituted by halogen, C₁-C₈ alkoxy, C₁-C₈ alkyl, NO₂, aryl or fused aryl.

8. Use according to claim 7, wherein the inhibitor is a compound having the formula (IV):



9. Use according to claim 1, wherein the inhibitor is a compound having the formula (V):



wherein:

A² is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₇ cycloalkyl, halogen, unsubstituted aryl, halogen-substituted aryl, fused aryl, NO₂, CN, NHR¹ and N(R¹)₂;

20

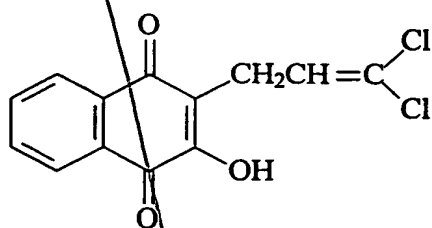
R¹ is selected from the group consisting of hydrogen, C₁-C₈ alkyl and OH;

X¹ is hydrogen or halogen; and

B¹, Y¹ and Z¹ are each independently selected from hydrogen, OH, C₁-C₈ alkyl, halogen, CN, NO₂ and CF₃.

25 10. Use according to claim 1, wherein the inhibitor is a compound having the formula (VI):

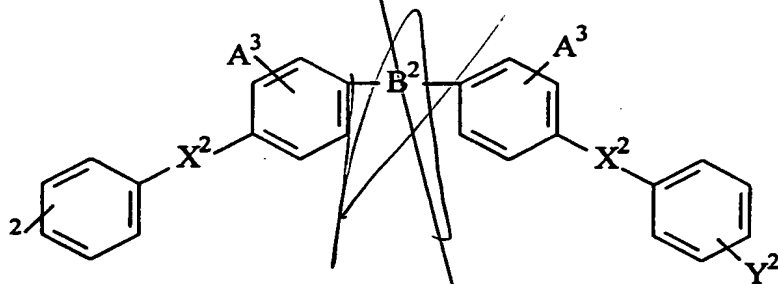
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(VI)

5

11. Use according to claim 1, wherein the inhibitor is a compound having the formula (VII):



(VII)

10 wherein:

each A^3 is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_{10} alkoxy, halogen and $N(R^2)_2$;

B^2 is a direct bond, $-CH=CH-$ or $-C\equiv C-$;

X^2 is selected from the group consisting of O, S and NR^2 ;

15 R^2 is selected from the group consisting of hydrogen, C_1-C_4 alkyl and aryl;

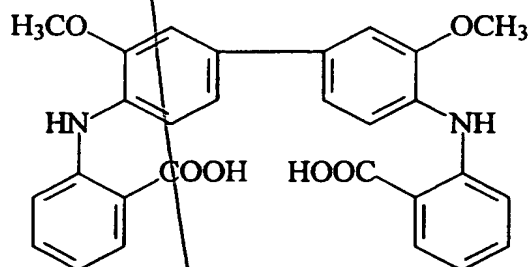
Y^2 is selected from the group consisting of $COOM^1$ and SO_3M^1 ; and

M^1 is selected from the group consisting of H, Li, Na, K and 0.5 Ca.

12. Use according to claim 11, wherein the inhibitor is a compound having the formula (VIII):

20

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(VIII)

- 10 13. Use according to any one of the preceding claims wherein the virus is a flavivirus selected from the group consisting of hepatitis viruses, yellow fever virus, West Nile virus, kunjin virus, dengue virus, St. Louis encephalitis virus, Japanese encephalitis virus, Murray valley encephalitis virus and tick-borne encephalitis virus.
- 15 14. A method according to any one of claims 1 to 13, wherein the virus is a rhabdovirus selected from vesicular stomatitis virus and rabies virus, or is the paramyxovirus RSV.
15. Use according to any one of the preceding claims wherein the medicament is for administration with an interferon.
- 20 16. Use according to any one of the preceding claims wherein the medicament further comprises an interferon.
17. Use according to claim 15 or 16, wherein the interferon is a human interferon.
18. Use according to claim 17, wherein the interferon is selected from the
- 25 group consisting of interferon $\alpha 2$, interferon $\alpha 8$ and interferon β .
19. Use according to claim 18, wherein the interferon is human interferon $\alpha 8$ having a specific activity of from 0.3×10^9 to 3×10^9 IU per mg protein.
20. Use according to claim 18, wherein the interferon is human interferon β having a specific activity of from 2×10^8 to 8×10^8 per mg protein.
- 30 21. Use according to any one of claims 15 to 20 wherein the inhibitor and the interferon are used in respective amounts which produce a synergistic effect.

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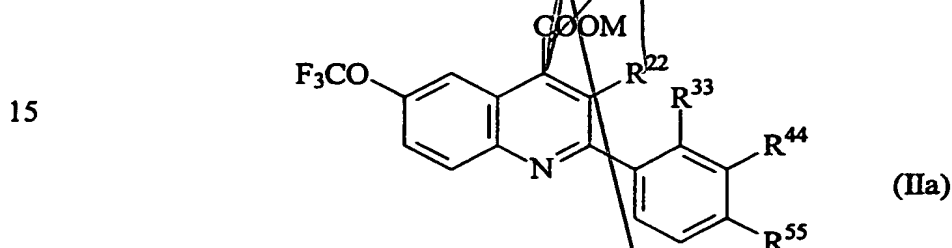
22. Use according to any one of the preceding claims wherein the medicament is for use with an inhibitor of a second enzyme selected from inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, cytidine triphosphate synthetase and S-adenosylhomocysteine hydrolase.

5 23. Use according to claim 22 wherein the medicament further comprises the inhibitor of the said second enzyme.

24. Use according to claim 22 or 23 wherein the inhibitor is mycophenolic acid, cyclopentenyl cytosine (CPE-C) or 3-deazaneplanocin A.

10 25. Use according to any one of claims 22 to 24 wherein the inhibitor of the second enzyme and the inhibitor of dihydroorotate dehydrogenase are used in respective amounts which produce a synergistic effect.

26. A compound of formula (IIa):



20 wherein

M is selected from the group consisting of H, Li, Na, K and 0.5 Ca;

R²² is H or C₁-C₆ alkyl;

R³³ is H or OR⁶ wherein R⁶ is H or C₁-C₆ alkyl;

R⁴⁴ is H or C₁-C₆ alkyl; and

25 R⁵⁵ is phenyl, cyclohexyl, phenoxy or benzoxy;
or a metabolite or prodrug precursor thereof..

27. A compound according to claim 26 which is selected from:

2-(4-biphenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K5);

2-(4-biphenyl)-3-methyl-6-trifluoromethoxy-quinoline-4-carboxylic acid

30 (compound I2K55);

2-(4-cyclohexylphenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound

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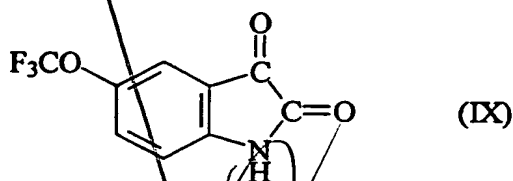
I2K46);

2-(4-benzyloxy-2-methoxy-3-methyl-phenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K51); and

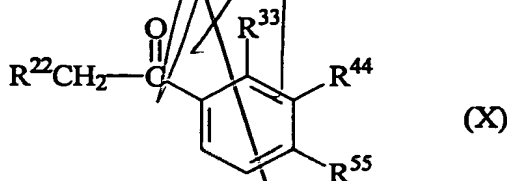
2-(4-phenoxyphenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K52).

28. A process for producing a compound of formula (IIa) as claimed in claim 26, which process comprises

a) condensing a trifluoromethoxy-substituted isatin compound of the following formula (IX):



15 with a ketone of formula (X):



wherein R^{22} , R^{33} , R^{44} and R^{55} are as defined in claim 26, in the presence of a base; and

(b) if desired, converting a resulting compound of formula (IIa) in which M is H into a pharmaceutically acceptable salt thereof wherein M is Li, Na, K or 0.5 Ca.

29. A method of treating a host infected with a virus of the Flaviviridae, Rhaboviridae or Paramyxoviridae family, which method comprises administering to the host an inhibitor of dihydroorotate dehydrogenase.

25 30. An anti-flavivirus, anti-rhabdovirus or anti-paramyxovirus agent comprising an inhibitor of dihydroorotate dehydrogenase.

31. Products containing an inhibitor of dihydroorotate dehydrogenase and

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an interferon as a combined preparation for simultaneous, separate or sequential use in treating an infection attributable to a virus of the Flaviviridae, Rhabdoviridae or Paramyxoviridae family.

32. Products containing an inhibitor of dihydroorotate dehydrogenase .
- 5 and an inhibitor of a second enzyme selected from inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, cytidine triphosphate synthetase and S-adenosylhomocysteine hydrolase as a combined preparation for simultaneous, separate or sequential use in treating an infection attributable to a virus of the Flaviviridae, Rhabdoviridae or Paramyxoviridae family.
- 10 33. Products according to claim 32 which additionally contain an interferon.
34. A method for identifying an anti-flavivirus, anti-rhabdovirus or anti-paramyxovirus agent, which method comprises:
- (a) providing a test compound;
- 15 (b) determining whether the test compound has activity as an inhibitor of dihydroorotate dehydrogenase; and
- (c) selecting the test compound as an anti-flavivirus, anti-rhabdovirus or anti-paramyxovirus agent if it is shown to have activity in step (b).

Add A2